

REMARKS

Claims 17-19 are pending. Claim 19 is canceled herein without prejudice. Claims 17-18 are amended to more clearly set forth aspects of the invention. Accordingly, claims 17 and 18, as amended, are under consideration.

Support for the amendments to the claims is found throughout the specification and in the original claims. Specifically, support for amendment to claim 17 is presented in original claim 17 and, for example, at page 4, lines 10-14 and in Figure 3, wherein support for a CLN2 polypeptide comprising SEQ ID NO: 3 is found; and at page 17, lines 22-28, wherein support for what is meant by at least 90% homologous is found; at page 43, lines 21-27, wherein support for intracranial administration is found; and at page 45, lines 4-16, wherein support for recombinant adeno-associated virus (AAV) vectors is found. Support for amendment to claim 18 is found in original claims 17 and 18 and at page 4, lines 10-14 and in Figure 3, wherein support for a CLN2 polypeptide comprising SEQ ID NO: 3 is found. No issue of new matter is introduced by the amendments to the claims.

The specification is amended herein to update the status of a prior application to which the present application claims priority and which has matured into a United States Patent. No issue of new matter is incorporated hereby.

Rejections under 35 USC § 112

Claims 17-19 are rejected under 35 USC § 112, first paragraph, for allegedly failing to comply with the enablement requirement. Claim 19 is canceled herein, thereby obviating any rejection of this claim. The Examiner is of the opinion that the breadth of the claims as previously presented reads on a broad genera of gene and protein therapy. In accordance with the amendments to the claims, the instant claims are directed to gene therapy. As a consequence, the comments presented in the Office Action that relate to protein therapy are hereby obviated. For the record, however, Applicant reserves the right to pursue claims directed to protein therapy at a later date. In view of the amendments to the claims and arguments presented herein, Applicant respectfully requests reconsideration of the rejection of the claims under 35 USC § 112, first paragraph, for an alleged lack enablement.

Responsive to the Examiner's assertions pertaining to an alleged lack of guidance as to (i) how a skilled artisan would have practiced the claimed method; and (ii) how the claimed method would have resulted in providing the CLN2 in deficient cells in an amount sufficient to treat an LINCL disorder, the Examiner is respectfully directed to a number of passages in the specification which teach the presently claimed method in sufficient detail for a skilled practitioner to practice the instant invention without undue burden. See, for example, page 43, line 21 through to page 46, line 5 of the specification. It is to be understood that a skilled practitioner would read such passages in the context of the art at the time of filing of the present application. Moreover, a skilled artisan would certainly have been aware of advances in the field of adeno-associated virus (AAV) vectors and methods relating to their use. See, for example, the references cited in the specification at page 45, lines 14-16 in the context of AAV vectors, such as Samulski et al., 1987, *J. Virol.* **61**:3096 and Samulski et al., 1989, *J. Virol.* **63**:3822-3828. See also, Davidson et al. (2000, *Proc. Natl. Acad. Sci.* **97**:3428-3432), submitted herewith for the Examiner's consideration, which summarizes some of the advances in the field of AAV vectors and their transduction capabilities in the central nervous system (CNS). It is also noteworthy that Davidson et al. cite multiple references available to the public in advance of the filing date of the present application which further attest to AAV vectors and their ability to direct long-term expression of transgenes in multiple tissues, including the CNS. See Davidson et al., page 3428, left column, first paragraph and references cited therein. Abstracts authored by Xiao et al. (1997, *Exp. Neurol.* **144**:113) and Clark et al. (1999, *J. Drug Target* **7**:269) are also enclosed for the Examiner's review as these references confirm the considerable information available to the skilled practitioner at the time of filing of the present application. Intracranial administration, as instantly recited, was also well within the capabilities of a skilled practitioner at the time of filing of the present application.

In support of the above assertions, Applicant submits the following post-filing references for the Examiner's consideration: Haskell et al., 2003, *Gene Therapy* **10**:34-42; Sondhi et al., 2005, *Gene Therapy* **12**:1618-1632; Hackett et al., 2005, *Human Gene Therapy* **16**:1484-1503; and Passini et al., 2006, *J. of Neuroscience* **26**:1334-1342. These references not only support the feasibility of the methods of the present invention,

but also underscore the high level of skill in the art at the time of filing of the present application as indicated by citations included in these post-filing references, some of which are mentioned herein. All four of these post-filing references present compelling evidence attesting to the utility and promise of AAV vectors for gene therapy via intracranial administration in general and, more particularly, with respect to gene therapy wherein levels of CLN2 polypeptide [otherwise known as lysosomal tripeptidyl peptidase I (TPP1)] are increased. The Passini et al. reference (2006, *J. of Neuroscience* 26:1334-1342), in particular, demonstrates that AAV-mediated delivery of CLN2 to the CNS results in a reduction in the pathological features of the LINCL in a mouse model of the disease and, therefore, supports AAV gene therapy to treat human patients afflicted with LINCL. See the entire reference. It is noteworthy that the two inventors of the present invention are authors on this paper, thereby demonstrating their continued efforts toward reduction to practice.

Regarding the state of the art at the time of filing, references cited in the above-mentioned post-filing references attest to significant advances achieved in the art with respect to AAV-mediated delivery to the CNS. See, for example, Sondhi et al. (page 1618, right column, first full paragraph), wherein compelling data are cited as suggesting that direct CNS administration of an AAV vector expressing CLN2 cDNA should be able to mediate expression of TPP-1 in a sufficient number of neurons to slow down, and potentially halt, the progression of the CNS disease. Numerous references are cited by Sondhi et al. to support the assertion that AAV gene transfer vectors are capable of mediating transfer and persistence of expression of a variety of genes in the CNS, including Kaplitt et al., *Nat. Genet.* 1994, 8:148-154; McCown et al., *Brain Res.* 1996, 713:99-107; During et al., *Gene Therapy* 1998, 5:820-827; Mandel et al., *J. Neurosci.* 1998, 18:4271-4284; Davidson et al., *Proc. Natl. Acad. Sci.* 2000, 97:3428-3432; Frisella et al., *Mol Ther.* 2001, 3:351-358; and Haskell et al., *Gene Therapy* 2003, 10:34-42. See also Passini et al. (page 1334, right column, first full paragraph), wherein the effectiveness of AAV vectors for the treatment of mouse and cat models of lysosomal storage disorders (LSDs) is described and citations affirming this contention are presented. Such citations include: Skorupa et al., *Exp. Neurol.* 1999, 160:17-27; Bosch et al., *Mol. Ther.* 2000, 1:63-70; Sferra et al., *Hum. Gene Ther.* 2000, 11:507-519; Frisella

et al., 2001, *supra*; Matalon et al., Mol. Ther. 2003, 7:580-587; Passini et al., J. Virol. 2003, 77:7034-7040; Passini et al., Mol Ther. 2005, 11:754-762; Cressant et al., J. Neurosci. 2004, 24:10229-10239; Desmaris et al., Ann. Neurol. 2004, 56:68-76; Griffey et al., Neurobiol. Dis. 2004, 16:360-369; Klugmann et al., Mol. Ther. 2005, 11:745-753; Rafi et al., Mol. Ther. 2005, 11:734-744; and Vite et al., Ann. Neurol. 2005, 57:355-364).

Sondhi et al. (page 1618, right column, first full paragraph through to page 1619) also state that the promise for treatment of LINCL via direct CNS administration of an AAV vector comprising CLN2 cDNA, which is capable of expressing TPP-1, is further supported by findings relating to mucopolysaccharidosis VII, a related lysosomal storage disease. In this regard, it is significant that mucopolysaccharidosis VII has been successfully reversed in a knockout mouse model by recombinant AAV2-mediated intracranial gene transfer. References cited in this context include: Frisella et al., 2001, *supra*; Skorupa et al., 1999, *supra*; Bosch et al., 2000, *supra*; and Sferra et al., 2000, *supra*.

Sondhi et al. (page 1619, left column, first paragraph continued from page 1618) also emphasize that a significant finding corroborating their assertion regarding the efficacy of direct CNS administration of an AAV vector expressing CLN2 cDNA in slowing LINCL disease progression is provided by the fact that a significant fraction of newly synthesized TPP-1 protein is secreted as pro-TPP-1, a 563 amino acid inactive form which can cross-correct nearby nontransduced cells through mannose 6-phosphate receptor-mediated uptake and subsequent activation in lysosomes to the 367 amino acid mature form. As indicated therein, the cross-correction between transduced and neighboring cells suggests that the effective range of gene transfer achieved is larger than expected [i.e., larger than the localized transduced region(s)]. The references cited by Sondhi et al. with respect to this conclusion are as follows: Lin et al., Biochem. J. 2001, 357:49-55; and Lin et al., J. Biol. Chem. 2001, 276:2249-2255.

The potential for AAV-mediated CLN2 gene delivery to the CNS to achieve long term robust transgene expression is summarized in a favorable light by Sondhi et al. on page 1627, right column, under the heading "Implications for future studies". Therein, During et al. (Hum. Gene Ther. 2001, 12:1589-1591) is cited, for example, as providing

evidence regarding short-term safety of AAV2-mediated therapeutic gene transfer into the brains of human patients via intracranial administration. Moreover, the Hackett et al. (2005, Human Gene Therapy 16:1484-1503) reference submitted herewith attests to the excellent safety record observed following direct administration of AAV2_{CUh}CLN2 to the brains of rats and nonhuman primates. See entire reference, in particular the Abstract and Discussion section starting at page 1499.

The Haskell et al. reference (2003, Gene Therapy 10:34-42) submitted herewith presents results indicating the feasibility of vector-mediated gene transfer of TPP-1 to the CNS as a potential therapy for LINCL. See Abstract and entire reference. More specifically, Haskell et al. examined the likelihood of gene transfer into mouse brain using recombinant adenovirus (Ad), feline immunodeficiency virus (FIV), and AAV vectors expressing TPP-1, after single injections into the striatum or cerebellum. For all three of the vectors tested, TPP-1 activity in brain homogenates was 3 to 7-fold higher than endogenous levels in the injected hemispheres. As indicated on page 39 (right column, first paragraph continued from left column), generally 1-5% of normal enzymatic levels are sufficient to achieve beneficial effects by enzyme replacement therapies with respect to other lysosomal disorders. In sum, these results suggest that therapeutic levels of TPP-1 are readily achieved using any one of these vectors.

Although the Examiner has cited a number of references in connection with this rejection, Applicant believes that issues raised in relation to these references are addressed herein and indeed, obviated via amendments to the claims and arguments as supported by references submitted herewith in a Supplemental Information Disclosure Statement. For the sake of completeness, a list of the references cited by the Examiner is as follows: Goodman & Gilman's "The Pharmacological Basis of Therapeutics", McGraw-Hill, New York, NY, pp. 77-101; Verma et al., 1997, Nature 389:239; Marshall, 1995, Science 269:1050; Carter et al., 2001, Br. J. Psychiatry 178:392; Shevtsova et al., 2004, Exp. Physiol. 90:53; Schuchman, 1999, Chemistry and Physics of Lipids 102:179; Barranger et al., 1999, Neurochem. Res. 24:601; Filion et al., 1997, Br. J. Pharmacol. 122:551; Davis, 2002, Curr. Opin. Biotech. 13:128; Cooper, 2003, Curr. Opin. Neurol. 16:121; and Scientific Consideration Related to Developing Follow-on Protein Products.

Divison of Dockets Management U.S. Food and Drug Administration, November 12, 2004, pp. 1-12.

In view of the amendments to the claims and clear evidence relating to the state of the art at the time of filing, Applicant asserts that the instant claims are sufficiently enabled by the specification for a skilled artisan to practice the claimed invention. Moreover, the post-filing references submitted herewith attest to the efficacy and safety of AAV-mediated gene transfer into mammalian brains, especially with respect to AAV-mediated transfer of CLN2. That being the case, Applicant respectfully requests reconsideration and withdrawal of the above-indicated rejection of the claims under 35 USC § 112, first paragraph.

Claims 17-19 are rejected under 35 USC § 112, first paragraph, for allegedly failing to comply with the written description requirement. Claim 19 is canceled herein, thereby obviating any rejection of this claim. The Examiner acknowledges that the specification describes the complete nucleic and amino acid sequences of human CLN2. Accordingly, claim 17 is amended to be directed to administration of a recombinant expression vector comprising a nucleic acid sequence encoding SEQ ID NO: 3 or a polypeptide comprising an amino acid sequence at least 90% homologous to SEQ ID NO: 3. In view of the amendment to claim 17 and ample written description for the instant claim as presented in the specification, Applicant respectfully requests reconsideration and withdrawal of the rejection based on an alleged lack of written description.

Claims 17-19 are rejected under 35 USC § 112, second paragraph, for alleged indefiniteness. Claim 17 is amended herein to clarify aspects of the invention. More specifically, claim 17 is amended to define the acronym LINCL as late infantile neuronal ceroid lipofuscinosis and to render the claim complete with respect to methodological steps. Claim 19 is canceled herein, thereby obviating any rejection of this claim. Applicant, therefore, believes that the amendments to claim 17 and dependent claim 18 are curative of the rejection based on alleged indefiniteness.

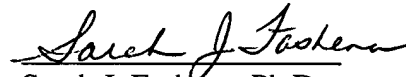
Fees

No additional fees are believed to be necessitated by this amendment. However, should this be an error, authorization is hereby given to charge Deposit Account No. 11-1153 for any underpayment or to credit any overpayment.

Conclusion

It is submitted, therefore, that the claims are in condition for allowance. No new matter has been introduced. From the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order, and such action is earnestly solicited. In the event that there are any questions concerning this amendment, or application in general, the Examiner is respectfully urged to telephone the undersigned so that prosecution of this application may be expedited.

Respectfully submitted,



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Enclosures: Petition for a One (1) Month Extension of Time
Supplemental Information Disclosure Statement